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EXAMINER	
DEJONG, ERIC S	

ART UNIT	PAPER NUMBER
1631	

DATE MAILED: 05/24/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/050,888	GESTELAND ET AL.	
	Examiner	Art Unit	
	Eric S. DeJong	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03/08/2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-64* is/are pending in the application.

4a) Of the above claim(s) *See Continuation Sheet* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4,8,10,12,13,17,18,22,23,25,29,31,33,34,38,39, and 43* is/are rejected.

7)☒ Claim(s) *20 and 41* is/are objected to.

8)☒ Claim(s) *1-64* are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 2 sheets
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

S.O.O.

Continuation of Disposition of Claims: Claims withdrawn from consideration are 3,5-7,9,11,14-16,19,21,24,26-28,30,32,35-37,40,42 and 44-64.

DETAILED ACTION

Election/Restrictions

Applicant's election of Group I (claims 1-43) and the election of Species (A), (D), (J), (M), (P), (R), (W), (Z), and (BB) satisfying the required first through ninth Species election requirements, respectively, in the reply filed on 03/08/2005 is acknowledged. Applicants submit that there would be no serious burden on the examiner to examine all claims regardless of whether or not a *prima facia* case of serious burden has been shown. However, since applicants have broadly asserted that there is no burden of search and did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 3, 5-7, 9, 11, 14-16, 19, 21, 24, , 26-28, 30, 32, 35-37, 40, 42, and 44-64 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention or species, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 03/08/2005. Claims 1, 2, 4, 8, 10, 12, 13, 17, 18, 20, 22, 23, 25, 29, 31, 33, 34, 38, 39, 41, and 43 are currently under examination.

Specification

The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. See for example page 20, lines 3 and 4 as well

as page 27, line 4. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

The specification is objected to as failing to provide proper antecedent basis for the claimed subject matter. See 37 CFR 1.75(d)(1) and MPEP § 608.01(o). Correction of the following is required:

Claims 8 and 29 recite the limitation "at least one hidden layer comprises from about 4 to about 16 hidden nodes". There is insufficient antecedent basis for this limitation in the instant specification.

Claims 12 and 33 recite the limitation "using a back-algorithm without a momentum term". It is acknowledged that the instant specification provides support for "the back-propagation momentum method generaliz(es) better than the basic back-propagation method" (see instant the specification, page 22, lines 4 and 5), however this does not provide sufficient support for "using a back-algorithm without a momentum term".

Claims 18 and 39 recite the limitation "using a binary threshold function with a cutoff in the range of about 0.01-0.50". There is insufficient antecedent basis for this limitation in the instant specification.

Claim Objections

Claims 20 and 41 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim.

Applicant is required to cancel the claims, or amend the claims to place the claims in proper dependent form, or rewrite the claims in independent form.

Claim 1, from which claim 20 depends, is drawn to a method of predicting antisense activity by employing an single artificial neural network. Claim 20 is more broadly drawn to predicting antisense activity by employing multiple (at least two or more) artificial neural networks. As such, claim 20 fails to further limit the subject matter of claim 1.

Claim 22, from which claim 41 depends, is drawn to a method of making an artificial neural network for predicting antisense activity. Claim 41 is more broadly drawn to employing multiple (at least two or more) artificial neural networks to predicting antisense activity. As such, claim 41 fails to further limit the subject matter of claim 1.

Claim Rejections - 35 USC § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> **The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.**

Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in Ex parte Forman, 230 USPQ 546 (BPAI 1986) and reiterated by the Court of Appeals in In re Wands, 8 USPQ2d 1400 at 1404 (CAFC 1988). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction presented, (3) the presence or absence of working examples,

(4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The Board also stated that although the level of skill in molecular biology is high, the results of experiments in genetic engineering are unpredictable. While all of these factors are considered, a sufficient amount for a *prima facie* case are discussed below.

Claims 4 and 25 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 4 and 25 recites "said input layer comprises only sequence motifs" in line 1 of the instant claims. Claim 1, from which claim 4 depends, and claim 22, from which claim 24 depends, defines the input layer as containing input nodes wherein "counts", broadly construed as the enumeration of sequence motifs present in a given nucleotide sequence, are entered (see the instant specification, page 11, line 19 through page 12, line 9). As defined by the instant claims and disclosed in the instant specification, the input layer cannot be comprised only of sequence motifs. As such, the above limitation recited in claims 4 and 25 renders one of skill in the incapable of making or using the neural network as claimed already comprises an input layer of input nodes and further requires entering counts into said input nodes.

Claim Rejections - 35 USC § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 13, 18, 34, and 39 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The use of the abbreviated term "ROC" in claims 13 and 34 cause the claims to be vague and indefinite and should be accompanied by an explicit definition when first recited in a set of claims. Use of abbreviated terms in claims that depend from and follow an explicit definition in a preceding claim is acceptable. For the purpose of continuing examination, the Examiner has construed the term "ROC" to mean Receiver Operating Characteristics.

The phrase "in the range of about 0.01-0.50" recited in claim 18, line 2 and claim 39, line 2 is a relative term which renders the claim indefinite. The range of "0.01-0.50" must be taken in context with the claimed binary threshold function, however the instant claim does not provide any definition of the units for said binary threshold function. As such, the phrase "in the range of 0.01-0.50" is indefinite as the units of the range are not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 2, 8, 10, 12, 17, 22, 23, 29, 31, 33, 38, and 43 are rejected under 35 U.S.C. 103(a) as being unpatentable over Matveeva et al. (IDS: Matveeva et al., Nature Biotechnology, 1998) taken in further view of Wu et al. (Nucleic Acids Research).

Matveeva et al. discloses several oligonucleotides that target various regions of C-raf mRNA and evaluate the binding efficiency of said oligonucleotides to C-raf mRNA taken in context of related antisense activity. See Matveeva et al., page 1374, column 2, line 12 through column 3, line 6 and Figure 1 (constructing a database comprising sequence data of oligonucleotides tested in vivo for activity in down-regulating expression of RNAs). Matveeva et al. additionally discloses the correlation coefficients

between intracellular and in vitro data for the oligonucleotides (activity data corresponding to said sequence data). See Matveeva et al., page 1374, column 3, lines 7-50 and page 1375, figure 2A.

(regarding claims 2 and 23) The reference of Matveeva et al. is contained in a publication of the scientific journal "Nature Biotechnology" (published articles). Further, Matveeva et al. discloses over 20 oligonucleotides with established *in vivo* antisense activity (results obtained with at least ten oligonucleotides). See page Matveeva et al., 1375, Figure 2A-C. An oligonucleotide that was not complementary to the C-raf mRNA was also used as a control (at least one mismatch or scrambled control oligonucleotide). See Matveeva et al., page 1374, Figure 1.

Matveeva et al. discloses that research establishing antisense activity for some oligonucleotides is only a step toward the challenging prospect of being able to predict antisense activity in cells using simplified model systems and that such data must be obtained and further analyzed with statistical methods for the future practical use of such assays (predicting antisense activity of an oligonucleotide for down-regulating expression of a selected RNA). See Mateeva et al., page 1375, column 2 line 3 through column 3, line 4. However, Mateeva et al. does not fairly teach the method of using or making artificial neural network systems for predicting the above described antisense activity of oligonucleotides for down-regulating expression of selected RNA as set forth in the instant claims.

Wu et al. discloses the methodology of using and developing an artificial neural network system for rapid and accurate classification of ribosomal RNA sequences

according to a phylogenetic relationship. See Wu et al., Abstract. Further, Wu et al. discloses that the major application of such neural networks is the rapid sequence annotation and automated family assignment which is a tool that is generally applicable to any databases that are developed according to family relationships. Such neural network designs are disclosed as being easily extended to the task of analyzing other nucleic acid sequences (a method for developing a neural network system for predicting biological activity of nucleic acid sequences; a method of making an artificial neural network). See Wu et al., page 4298, column 2, lines 13-42.

Wu et al. discloses that the systems and software for the neural network have been ported to several different computer platforms and computer languages (developing an artificial neural network embodied on a computer-readable medium). See Wu et al., page 4293, column 2, lines 42-57. The disclosed neural network system is configured as a three layer network comprising an input layer, a hidden layer, and an output layer each containing a variable number of nodes (providing an input later containing a selected number of input nodes; providing at least one hidden layer comprising a plurality of hidden nodes having full connectivity to said input nodes; an output layer comprising at least one output node connected to said plurality of hidden nodes) See Wu et al., Figure 1 and page 4292, column 1, lines 20-32. A nucleic acid sequence is first converted by an encoding method into a neural net input vector (broadly construed as a count for a given sequence motif; entering counts for each of said sequence motifs; entering activity data correlated with said counts), and the neural network then maps the sequence vectors into predefined classes according to

sequence information embedded in the neural interconnections after network training (mapping sequence motifs; training the artificial neural network). See Wu et al., see Figure 1 and page 4292.

(regarding claims 8 and 29) Wu et al. discloses in Figure 1 at least 4 nodes in the hidden layer that under a reasonably broad interpretation is comprises about 4 nodes. Additionally, Wu et al. discloses that in counter-propagation neural network, the number of nodes in the hidden layer is dynamically controlled and can be added to in order to optimize pattern recognition in the system (at least one hidden layer comprises from about 4 to about 16). See Wu et al., page 4293, column 2, lines 13-41.

(regarding claims 10 and 31) Wu et al. discloses in Figure 1 that the output layer is comprised of a variable number of individual nodes output nodes. Since individual nodes make up the out put layer, a reasonably broad interpretation is that the output layer comprise one output node as instantly claimed.

(regarding claims 12 and 33) Wu et al. teach an embodiment of the sequence classification/clustering system of the neural networks include a back propagation neural network, which includes a momentum term. However, the values of the momentum term are varied between –0.3 and 0.3 to optimize a particular neural network system. A momentum term of 0, which is an embedment of the disclosed system, would reasonably be construed as a back propagation algorithm and read on the claims neural network using a back-propagation algorithm without a momentum term. See Wu et al., page 4293, column 1, lines 40-56. Wu et al. cites the additional reference Wu et al. (Protein Science) in support of the above methodology of using a

back propagation algorithm. See Wu et al., Protein Science, page 669, column 1, lines 25-36.

(regarding claims 17 and 38) The instant specification discloses an example of how output data may be normalized utilizing a function that forces the result to lie in the range of 0 to 1. See the instant specification, page 22, lines 10 and 11. Relying on this example, the examiner has construed that a reasonably broad interpretation of normalization is a function or operation that rescales a data to the range of 0 to 1. Wu et al. in Figure 1 demonstrates that sequence data converted into a compressed input vector wherein amplitude values are made to conform to a range of 0 to 1 (said counts of sequence motifs are entered as normalized data).

(regarding claim 43) Wu et al. discloses that the systems and software for the neural network have been ported to several different computer platforms and computer languages (an artificial neural network embodied on a computer-readable medium). See Wu et al., page 4293, column 2, lines 42-57.

Taken in view of Wu et al., it would have been obvious to one of skill in the art to rely on the application of the above disclosed neural networks the purpose of predicting antisense activity of an oligonucleotide for down-regulating expression of a selected RNA, constructing a database comprising sequence data of oligonucleotides tested in vivo for activity in down-regulating expression of RNAs, and activity data corresponding to said sequence data as taught by Matveeva et al.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Eric S. DeJong whose telephone number is (571) 272-6099. The examiner can normally be reached on 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel, Ph.D. can be reached on (571) 272-0718. The fax phone number for the organization where this application or proceeding is assigned is (571) 272-8300.

Any inquiry of a general nature or relating to the status of this application should be directed to Legal Instrument Examiner, Tina Plunkett, whose telephone number is (571) 272-0549.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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Ardin H. Marschel 5/16/05
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PRIMARY EXAMINER